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ACROSCLEROSIS : A DISEASE *SUI GENERIS* OR A VARIETY OF DIFFUSE SCLERODERMA ?

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THE term " acrosclerosis " has wide currency in general medical and dermatological literature. So has Sellei's view (1931, 1934, and 1936), subsequently confirmed by O'Leary and Waisman (1943) and recently by Ingram (1958), that acrosclerosis is a disease *sui generis* and not Raynaud's syndrome coexistent with diffuse scleroderma, as was originally assumed by Hutchinson (1893, 1896). The recognition of the disease as an entity is based on the association with Raynaud's phenomenon, which may precede, or occur simultaneously with the induration, and the distribution of lesions on the hands (occasionally the feet) and face.

According to Ingram, diffuse scleroderma differs in that it does not begin on the fingers but on the wrists and is proliferative, i.e. it does not leave atrophy or cause trophic ulceration of the distal phalanges of the fingers. The sclerodactylous changes on the hands very much resemble those of acrosclerosis, but the mask-like facies differs from the facial changes in acrosclerosis, which result from atrophy leading to thinning and radial furrowing of the lips and a pinched nose without true induration of the skin, which is nevertheless drawn and taut. In scleroderma, visceral changes are of the same type as in acrosclerosis, but they are rather rare and never so pronounced. Ingram says diffuse scleroderma may become stationary or may even clear, whereas acrosclerosis is progressive and fatal. This is unlike the earlier view (O'Leary and Waisman, 1943 ; Sellei, 1936) that acrosclerosis runs a slow course, often becomes stationary and carries a much more favourable prognosis than diffuse scleroderma, which leads relatively rapidly to complete immobilization (" *homme momnié* ").

Views also differ with regard to the nature of the skin changes ; according to Ingram they consist of atrophy and loss of tissue, but according to Sellei of shrinkage, stiffening and induration of the skin and eventual complete loss of

its mobility. Furthermore, Sellei says there are frequent changes in, and wasting of, muscles, whereas other authors claim muscle wasting to be frequent in true scleroderma, but rare in acrosclerosis (O'Leary and Waisman, 1943 ; Truelove and Whyte, 1951 ; Littler and Canter, 1951).

As regards pathogenesis, Sellei suggests that acrosclerosis is an angiotrophoneurosis and depends on disturbances in the central and peripheral nervous systems, whereas in scleroderma there are no changes in the vessels and autonomic nervous system. Littler and Canter (1951) emphasize a connection between acrosclerosis and the autonomic nervous system and endocrine glands, the adrenals in particular. Ramsay (1951) believes it to be an adaptation disease and Ingram thinks it is a primary degenerative vascular disease which should correctly be called " progressive systemic arteriolar degeneration ". Unlike in scleroderma, collagen changes are secondary, and therefore the disease is not collagenous but primarily vascular.

Since the classification of acrosclerosis and its relation to diffuse scleroderma are unclear and different views exist as to its clinical features and diagnostic criteria, we have analyzed our cases of diffuse scleroderma with especial reference to cases with attendant Raynaud's phenomenon.

In an earlier report (Jabloński, Bubnow and Lukasiak, 1958) we demonstrated that in the course of long-standing Raynaud's disease, the fingers may show scleroderma-like changes which have to be distinguished from true scleroderma since they are not progressive and are not attended by a mask-like facies or visceral changes. We have shown that sensory chronaxy is prolonged in the entire skin even in the very earliest stages of scleroderma restricted to the hand, whereas in scleroderma-like changes it is normal outside the areas affected (Jabloński, Bubnow and Lukasiak, 1957). We have also found that Raynaud's phenomenon often but not invariably accompanies or precedes acroscleroderma (true scleroderma) and may be revealed by a characteristic capillaroscopic picture.

This paper is intended to prove that acrosclerosis is a variety of scleroderma with marked symptoms of angioneurosis but not a disease *sui generis*.

Material.

Our material included 45 cases of diffuse scleroderma, 33 of which were of the acroscleroderma type. In all, there were symptoms typical of both acrosclerosis and diffuse scleroderma which therefore cannot be considered to be two separate entities. Most were of the acroscleroderma type, i.e., they were accompanied or preceded by Raynaud's phenomenon and the skin changes began on the hands, or hands and face, except for one case where they began on the face. Women predominated : of the 33 cases only 5 were in men of which one was very atypical. In only 3 cases of acroscleroderma were the

changes restricted to the hands and face ; in two the symptoms corresponded to acrosclerosis. In one case the hands showed not atrophy, but indurated oedema and in another the face and hands were typical of scleroderma and the disease ran a rapid course. In the remaining cases the changes spread at various rates, involving consecutively the neck, thorax, occasionally the whole trunk and lower extremities.

Visceral Changes.

In 18 of the 33 cases there were visceral changes (Table I), viz., dysphagia, radiologically established functional or anatomical abnormalities in the oesophagus, stomach and intestines, cardiac symptoms, electrocardiographic signs of infarction, or disease of the lungs.

Table I.—*Visceral Involvement in Relation to the Extent of Skin Changes.*

	Acroscleroderma.		Diffuse scleroderma other than acroscleroderma.	
	Generalized changes.	Changes not generalized.	Generalized changes.	Changes not generalized.
Visceral changes . . .	13	5	7	0
No visceral changes . .	7	8	2	3
Total cases	20	13	9	3

However, in seven of the remaining twelve cases other than acroscleroderma, visceral involvement was of the same type and usually more pronounced. In our material, visceral changes were noted chiefly in the cases with generalized skin lesions, 20 out of 25 cases showing visceral involvement, which contradicts claims that lesions affecting the whole body are not accompanied by visceral sclerosis.

Visceral involvement does not appear to depend on the speed with which the disease progresses ; it is more frequent in cases of rapidly developing scleroderma of a type other than acroscleroderma, but in acroscleroderma it occurs both in slowly and rapidly developing cases and more frequently in long-standing ones (Table II).

Table II.—*Visceral Involvement in Relation to the Course Run by the Disease.*

	Acroscleroderma.		Scleroderma other than acroscleroderma.	
	Rapid course.	Slow course.	Rapid course.	Slow course.
Visceral changes . . .	7	11	5	2
No visceral changes . .	11	4	2	3

The Hands.

The hands were involved in almost all cases of diffuse scleroderma of either type, even where the induration did not begin on the hands and was neither

preceded nor accompanied by Raynaud's phenomenon. This agrees with Ingram's view that in scleroderma changes on the hands show features resembling acrosclerosis and even make distinction impossible. However, Ingram believes that in true scleroderma there is never ulceration of the finger tips with resorption of distal phalanges, which he considers to be a typical feature of acrosclerosis.

Trophic changes were noted in 14 of the 33 cases of acroscleroderma and in 5 of the 12 cases of diffuse scleroderma of a type other than acroscleroderma (Table III). It follows that resorption of the distal phalanges and ulceration of the finger tips does not provide a basis for distinguishing acrosclerosis from the group of scleroderma.

TABLE III.—*Trophic Changes and Ulceration of Terminal Phalanges.*

	Acroscleroderma.		Scleroderma other than acroscleroderma.
	Generalized changes.	Changes not generalized.	
Trophic ulceration of the finger tips . . .	11	3	5
No trophic ulceration of the finger tips . . .	9	10	7

THE FACE.

In acrosclerosis, facial changes are said to be purely atrophic and to cause wasting of the subcutaneous tissue, thinning and furrowing of the lips and pinching of the nose, but are said never to be sclerodermatous. Table IV shows that facial changes cannot be used as a basis for distinguishing between acrosclerosis and true scleroderma, since the sclerotic changes are usually accompanied by atrophic ones ; however, the changes may also be exclusively sclerodermatous in either form of scleroderma.

TABLE IV.—*Facial Changes.*

Facial changes.	Acroscleroderma.	Diffuse scleroderma other than acroscleroderma.
Atrophic and sclerodermatous changes	14	6
Chiefly atrophic changes .	9	1
Sclerodermatous changes .	10	5
Total .	33	12

THE JOINTS.

The authors who favour the recognition of acrosclerosis as an entity say that articular changes and radiological symptoms typical of scleroderma are found in both acrosclerosis and true scleroderma. But pronounced stiffening of the joints and their eventual immobilization are said to be absent in acro-

sclerosis and to constitute an essential feature of true scleroderma. In our material typical radiological changes were found in both acroscleroderma and diffuse scleroderma of the other type. Stiffening and immobilization of the joints was noted in either form and depended chiefly on the extent of skin changes and the severity of the course. We noted stiffening of joints in 5 cases of generalized acroscleroderma and in 6 cases of diffuse scleroderma of the other type. Radiological findings were in most cases characteristic of scleroderma and in 5 cases (3 of the acroscleroderma type and 2 of the other) they revealed features of polyarthritis chronica evolutiva with distinct narrowing of the articular space, subchondral resorption of bone or destruction of joints. Such cases we consider to have coexistent scleroderma and polyarthritis. This shows that advanced immobilization of joints cannot provide a basis for distinguishing acrosclerosis from true scleroderma. Of two cases of "*homme mommié*" (or rather "*femme mommiée*"), one showed the features of acroscleroderma and the other those of the typical diffuse scleroderma. Severity of articular changes, with even total immobilization, depends exclusively on the course of the disease, but not on the type of diffuse scleroderma.

We noted muscular involvement in either type of scleroderma in cases with widespread changes causing shrinkage and loss of mobility of skin. Muscle biopsy performed in 6 cases revealed changes characteristic of scleroderma, namely proliferation and hyalinization of the intermuscular connective tissue with secondary atrophy and occasional degeneration of muscle fibres.

Course.

A slow course is said to be characteristic of acrosclerosis and a rapid one of diffuse scleroderma. This difference was not conspicuous in our material, although some may be noted (Table V). In cases of acroscleroderma a slow course of the disease was more frequent than in diffuse scleroderma of different type, although skin changes spread rather rapidly in most cases; however, the course may also occasionally be prolonged in cases of scleroderma of the type other than acroscleroderma. In acroscleroderma, relatively favourable

Table V.—*Development of the Disease and Results of Treatment.*

	Acroscler-oderma.	Diffuse scleroderma other than acroscleroderma.	Notes.
Slow course	15	4	—
Rapid course	18	8	—
Treatment effective (development arrested)	11	1	In 4 cases results of treatment unknown (patients failed to return, or observation period too brief).
Treatment ineffective (disease progressing or stationary)	20	9	
Fatal termination	2	2	—

response to treatment is more frequent, especially as regards arresting progress of the disease, but in most cases the process continues to develop despite treatment.

Death in two cases of acroscleroderma was connected with pseudo-infarctive changes in the heart ; in one case of scleroderma of different type it was preceded by several years of total immobilization of the patient, while in another it was the result of the very rapid course of the disease (no autopsy was made since the latter two patients died at home). In nine patients there were the electrocardiographic changes of old infarcts and one died subsequently with symptoms of infarction. In these 9 cases there were 5 with acroscleroderma and 4 with scleroderma of different type ; in the latter, Raynaud's phenomenon was never noted. This shows that prognosis is equally grave in so-called true scleroderma and in so-called acrosclerosis ; in either, death may occur from visceral changes, especially in the heart muscle.

Chronaxy.

Our survey covers also sensory chronaxy, with the exception of four cases which were treated before we performed chronaximetry routinely in all cases of scleroderma. Irrespective of type and extent of sclerodermatous changes, sensory chronaxy was in all cases invariably prolonged over the entire surface of the body, which is pathognomonic for scleroderma and may serve as evidence in the differential diagnosis of clinically doubtful cases. When changes are widespread and progressive, chronaxy is conspicuously prolonged. Successive measurements make possible the evaluation of the course run by the disease and are important in prognosis. When the changes are stationary and do not spread, the chronaxy indices are relatively low and in consecutive measurements show no tendency to rise. When chronaxy is successively prolonged, prognosis is unfavourable even when there is a temporary remission after treatment. Chronaxy is prolonged in both acroscleroderma and scleroderma of different type without concomitant Raynaud's phenomenon. In long-standing Raynaud's disease, when there are merely indurated oedema of the hands, exclusively atrophic changes and telangiectases in the face, it is often very difficult to determine on clinical evidence alone whether the skin changes are due to trophic disturbances accompanying Raynaud's disease, or to early acroscleroderma developing in the course of Raynaud's disease. Usually a correct diagnosis is made in these cases only after several years' observation and when sclerotic changes typical of scleroderma appear in the skin and internal organs. Sensory chronaximetry, however, makes early diagnosis possible before clinical changes are characteristic. Two patients showed such early clinical changes and Raynaud's disease had been diagnosed elsewhere, but chronaxy was prolonged even in the apparently healthy skin (although the

indices were relatively low) and the further course of the disease revealed typical acroscleroderma. This question, which is of considerable importance in practice, will be dealt with separately.

In the preceding report we assumed in agreement with Allen, Barker and Hines (1946) that Raynaud's phenomenon precedes scleroderma only slightly, rarely by more than 10 to 20 months. Our material leads us to conclude that it may precede scleroderma by even more than 10 years and that acroscleroderma may develop in every case of long-standing Raynaud's disease. These cases appear to run a slower and relatively milder course, but generalized sclerosis is not infrequent and later on the course may be rapid. Chronaxy indices were high in rapidly developing cases and showed either a tendency to rise or remained at the same level, with one exception, where chronaxy became slightly shortened after treatment and a clinical improvement was noted.

Capillaroscopy.

Capillaroscopy was typical for Raynaud's syndrome with concomitant scleroderma, for scleroderma, and exceptionally for Raynaud's disease (Table VI).

Table VI.—*Capillaroscopy.*

Type of scleroderma.	Patterns typical for: Raynaud's phenomenon and scleroderma.	Patterns typical for: Scleroderma.	Patterns typical for: Raynaud's disease.	Cases not examined by capillaroscopy.
Acroscleroderma . .	16	9	4 .	4
Diffuse scleroderma other than acroscleroderma .	3	8	— .	1

In acroscleroderma the changes have usually the features of Raynaud's phenomenon with concomitant scleroderma, although in a substantial proportion of cases they have features exclusively characteristic of scleroderma. It has to be assumed that at some stages, early ones especially, coexistence of Raynaud's phenomenon is more frequent. In a fairly large proportion of cases of acroscleroderma capillaroscopy reveals no Raynaud's phenomenon, but in the type of scleroderma in which involvement of the hands is secondary, there may be occasional Raynaud-type loops. This is still another proof that there are no essential differences between the two forms of scleroderma and that Raynaud's phenomenon may occur at times in either, even when involvement of the hands is secondary, although it is more frequent in acroscleroderma where Raynaud's phenomenon either precedes or accompanies sclerodermatous changes.

Pathogenesis.

The alleged differences in pathogenesis between the two types appear to be unfounded. Ingram believes true scleroderma to be a primary proliferative

collagenosis and acrosclerosis a primary degenerative vascular disease with secondary trophic cutaneous changes. He proposes therefore the name progressive systemic arteriolar degeneration and includes it, as regards classification, in Raynaud's disease. Our investigations show sensory chronaxy to be prolonged over the entire surface of the body including the apparently normal skin in all cases of scleroderma, irrespective of extent and distribution of the lesions and presence or absence of Raynaud's phenomenon, which suggests identity of pathogenesis. Prolonged chronaxy in the entire skin is pathognomonic for scleroderma since it is noted in no other dermatological or neurological conditions. Further investigations are in progress to determine the level of the nervous system at which the disturbances responsible for scleroderma originate. The results so far available suggest that these lesions involve the subcortical autonomic centres. Neurohistological investigations (John, 1949 ; Ormea, 1952 ; Marchionini and Thiess, 1958 ; and others) indicate primary involvement of the vegetative nervous system in the skin, which precedes perceptible disorders in collagen. Oesophageal changes noted in different types of diffuse scleroderma and frequently in acrosclerosis are attributable in the early stages to disturbances in the function of the autonomic nervous system diminishing peristalsis ; later there is atrophy of the muscularis, induration, ulceration, and constriction (Hale and Schatzki, 1944 ; Olsen, O'Leary and Kirklin, 1945 ; Littler and Canter, 1951 ; Zgliczyński, 1952 ; Dowling, 1955 ; Delacrétaz and Pasquier, 1957 ; Bettley, 1958 ; and others). Zgliczyński studied in detail the radiological changes in the alimentary tract in six of our cases of diffuse scleroderma of which two corresponded to so-called acrosclerosis and four to scleroderma of different type. The nature of the abnormalities indicated disorders of the autonomic nervous system and a neurovegetative origin of diffuse scleroderma irrespective of associated or preceding Raynaud's phenomenon.

Visceral changes, atrophic, sclerodermatous or ischaemic, are found in all types of diffuse scleroderma (Matsui, 1924 ; Talbott *et al.*, 1939 ; Lushbaugh, Rubin and Rothman, 1948 ; Skouby and Teilum, 1950 ; Duffy, 1951 ; Dowling, 1955 ; de Gennes *et al.*, 1957 ; and others). Autopsy was made in two of our cases and revealed advanced pseudoinfarct in the heart, glomerulonephritis and changes in the alimentary tract with erosions in the oesophagus and stomach. These two cases, although of the acroscleroderma type, are wholly atypical of acrosclerosis (generalized cutaneous involvement and rapid course ; in one onset with facial sclerosis and subsequent involvement of the entire skin).

In all cases of scleroderma, there are obliterative arteriolar changes and this is diagnostically important, especially in diffuse scleroderma (Brown *et al.*, 1930 ; O'Leary and Nomland, 1930 ; O'Leary *et al.*, 1957). Plethysmography (Longhi, 1944) and reflex thermometry curves, or those of rewarming

(Jabłońska *et al.*, 1957) indicate distinct vascular changes in scleroderma and these resemble those found in sympathectomized extremities.

Both Raynaud's disease and scleroderma appear to be connected with the autonomic nervous system (Brody and Bellin, 1937), the former being an angioneurosis and the other essentially a trophic disorder involving also—but not exclusively—the vascular system. Prolonged sensory chronaxy in the entire surface of the body, so characteristic of scleroderma, is never noted in Raynaud's disease. We obtained it in healthy subjects after administration of chlorpromazine and ganglion-blocking preparations and it may also be found in sympathectomized extremities (data to be published).

It has to be assumed that in scleroderma there is injury of the central autonomic nervous system, with corresponding cutaneous changes. Raynaud's disease, on the other hand, is probably essentially a disorder of the sympathetic nervous system consisting of the excessive excitability of vasoconstrictor nerves. Whether it is due to disturbances in the function of intermediolateral cells of the thoracolumbar section of the spinal cord or of higher centres, for instance the hypothalamus, is still obscure. In scleroderma, disturbances in the function of vasomotor nerves do not constitute the basis of the disease, although vasoconstriction may precede or coincide with sclerotic changes. Lesions of the nervous system are more extensive and not restricted to the sympathetic vasomotor system. However, the nature of the neurovegetative disturbances in scleroderma calls for further investigations.

Conclusions.

1. An analysis of 45 cases of diffuse scleroderma leads us to conclude that acrosclerosis is a variety of diffuse scleroderma preceded or accompanied by Raynaud's phenomenon.

In all but three of the cases described there were simultaneous features characteristic of both so-called acrosclerosis and diffuse scleroderma, which made distinction between the two diseases impossible.

Generalization of the sclerotic changes in the skin may occur in any case of scleroderma, including those which begin in the hands and are preceded or accompanied by Raynaud's phenomenon.

Diffuse scleroderma without Raynaud's phenomenon also usually begins in the hands and face.

Atrophic changes in the face, viz. thinned and furrowed lips and pinched nose, usually accompany sclerodermatous changes and are not specifically distinctive of acrosclerosis.

Trophic digital changes, such as ulceration or resorption of the distal phalanges, may occur in every case of diffuse scleroderma which involves also the hands and are not a specific feature of acrosclerosis.

Visceral involvement, viz., changes in the oesophagus and gastrointestinal tract, heart muscle, lungs and kidneys, may occur in any type of diffuse soleroderma and not only in acrosclerosis.

The course run by scleroderma with concomitant or preceding Raynaud's phenomenon may be rapid (although frequently prolonged) and that of the different type of scleroderma may occasionally be slow, which makes differential diagnosis on the basis of the rate of progress impossible.

Pronounced stiffening of the joints is found in either form of diffuse scleroderma (although more often in the form other than acroscleroderma) and depends exclusively on the extent of changes and severity of the course.

The character of articular and muscular changes is the same in either form of diffuse scleroderma, irrespective of presence or absence of Raynaud's phenomenon.

The histological picture of the cutaneous changes is the same in either form of scleroderma.

Sensory chronaxy is prolonged over the entire surface of the body in either type of scleroderma.

2. Cases beginning with changes in the hands and face, with concomitant or preceding Raynaud's phenomenon, ought to be described as acroscleroderma to stress the predominance of changes in the extremities. However, acroscleroderma is but a variety of diffuse scleroderma.

3. In long-standing Raynaud's disease, lasting even for many years, scleroderma may develop. This development is often very slow and the course relatively mild, but the danger of generalization of the sclerodermatous changes in the skin and of visceral involvement is always there. In determining whether some skin changes in Raynaud's disease mark the beginning of scleroderma, chronaximetry is of fundamental importance ; sensory chronaxy is prolonged in the entire seemingly healthy skin even in the earliest stages of scleroderma.

4. Sensory chronaxy is also very important for prognosis ; successive distinct and increasing prolongations indicate rapid development of the disease, whereas diminution is a favourable symptom. An exception must be made for changes in the heart, which may cause fatal termination in spite of improvement in the skin and of declining chronaxy indices.

5. Raynaud's phenomenon accompanying scleroderma indicates abnormally increased excitability of vasoconstrictor nerves. The pathogenesis of scleroderma, although still obscure, is probably connected with damage of higher autonomic nervous centres, among others those exerting vasomotor control.

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ORAL EPITHELIAL NAEVI.

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Since 1956, when one of us (B.E.D.C.) reviewed the literature on oral epithelial naevi and reported six cases, two further papers have been published. Zegarelli and Kutscher (1957) described three patients under the title " familial white folded hypertrophy of the mucous membranes ". These were a thirty-one year old woman and her six and ten year old sons whose oral mucosae had a grayish-white corrugated appearance. The cheeks mainly were affected. Similar involvement of the vaginal mucosa was observed in the mother. Histological examination of both the oral and vaginal mucosae showed considerable vacuolisation of the prickle cells. Darling and Fletcher (1958) described under the title " familial white folded gingivostomatosis " four patients in two generations of the same family. In the most severely affected, a woman of twenty, the buccal and lingual mucosa appeared white, sodden and furrowed and histological examination of the buccal mucosa showed marked hydropic degeneration of the deeper prickle cells and irregular parakeratosis.

The case to be described is similar to those recently published except that so far as can be ascertained no relations are affected.

Case Report.

A man aged twenty-eight, had been aware of having a " white mouth " since the age of twelve. Thrush had been diagnosed on two occasions, but no other relevant information has been obtained. No other member of his family was apparently affected. The feeling of roughness of his cheeks varied not only from day to day, but from one part of a day to another : otherwise the condition was symptomless.

On examination, the appearance of the oral mucosa could best be described as having a white folded spongy appearance, looking sodden in places that were subject to mild friction from the teeth. (Fig. 1). The cheeks, lower buccal sulcus, gingivae distal to 8 | 8, anterior pillars of fauces, ventral surface of lateral margin of tongue, dorsum of tongue and to a less extent the lips were affected. There was no loss of suppleness and the white sodden covering could be wiped off without leaving a bleeding surface (Fig. 2). No extra-oral lesions were discovered. Wassermann and Kahn reactions were negative.

A biopsy of the left cheek was performed below the occlusal line near the left commisure. Histological examination showed marked parakeratosis and acanthosis with hydropic degeneration of prickle cells (Fig. 3). The basal layer was intact and

FIG. 1.

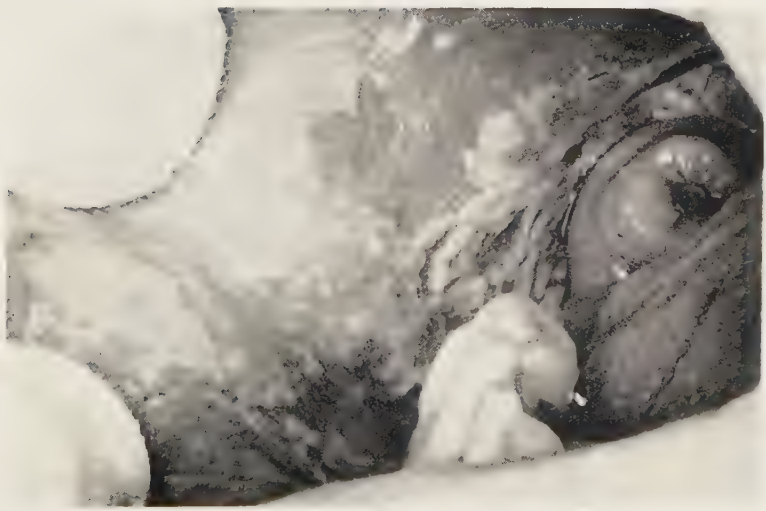

FIG. 2.

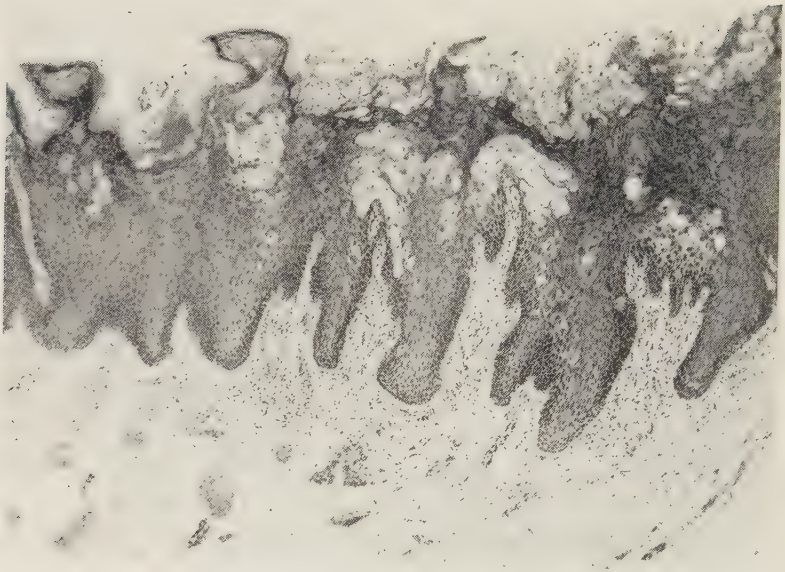

FIG. 3.

FIG. 4.

well defined and the hydropic degeneration of the prickle cells was patchy in distribution. Where this was most in evidence there was irregular parakeratosis giving the surface a craggy appearance (Fig. 4). There was a light subepithelial chronic inflammatory infiltration in keeping with that usually seen in the part of the buccal mucosa subject to mild friction.

Discussion.

It is becoming apparent that there are two or possibly more clinical entities grouped under the title oral epithelial naevus.

The first as described by Cooke (1956) is characterized by a wrinkled white patch of the oral mucosa resembling the undulations left on the sand by the ebbing tide. On histological examination the affected epithelium is well keratinised without any accompanying subepithelial infiltration of the corium. Five of the six cases reported in that paper were in this category. No family history of the disorder was discovered in any of them and only localised areas of the mucosa were affected, generally symmetrically. In these cases there appears to be a simple developmental defect.

The second group is that with which this paper is primarily concerned and the term often used in the literature, familial white folded gingivostomatosis, describes it well. The case reported here is an example of this entity although no family history was ascertained. Cooke (1956) believed his Case 5 (a woman aged 18 whose two brothers and two sisters were also affected) to be different from the others and thought it simulated the cases reported by Everett and Noyes (1953) who described this condition in two brothers under the title "white folded gingivostomatsois." There is often a family history and if most of the mucosa is affected the condition may be noticed at birth or soon after. The cheeks are most extensively involved, the tongue less but no part of the oral mucosa is immune. While the condition is generally symmetrical, it may be unilateral. It is a common finding that the mouth may feel rougher at different times of the day and it often feels most rough early in the morning. Gandy (1952) described a case in a woman aged 20 who had always had a white mouth and whose family on the maternal side was also affected; the white sodden areas of the mucosa could be wiped off without causing haemorrhage. This feature was also noted in the present case.

The histological appearance is almost identical to that found by Darling and Fletcher and their description of the irregular parakeratosis giving a shaggy appearance to the surface is apt. Hydropic degeneration is not an uncommon finding in the prickle cells of the oral mucosa, but it is a distinctive and constant finding in these cases. Interfering as it does with the process of keratinisation to produce irregular parakeratosis, it may be regarded as the cardinal histological feature.

It is interesting to note that monilial infection was incriminated on two occasions and that in one of the cases of Darling and Fletcher monilia was

grown repeatedly. That the white patches can be wiped off the mucosa is of course also like moniliasis. No doubt monilial infection is superimposed from time to time on the abnormal mucosa, but the length of history and the absence of inflammatory changes in the mucosa should exclude moniliasis as the cause of this condition. The age incidence, absence of symptoms and the manner in which the white patch can be removed from the mucosa differentiate these cases from reactions to friction, smoking and other irritants that are often grouped under the title leucoplakia. On histological examination, the intense inflammatory reaction of the corium so characteristic of leucoplakia is not seen.

Familial white folded stomatosis is a good descriptive title for this subdivision of epithelial naevi. The clinical and histological differences between these two subdivisions is based on the fact that in one group the process of keratinization is complete, while in the other it is not, resulting in parakeratosis. The jig-saw puzzle of developmental anomalies of the oral mucosa showing keratinization is slowly being pieced together and it is not yet possible to say how this abnormal mucosa will react when subjected to irritation by localised friction, smoking, alcohol, spices etc. Opinion must remain *sub judice*, as to whether there is a greater or lesser chance of neoplasia supervening compared with other diseases of the oral mucosa showing keratinization but so far everything tends to support the belief that an epithelial naevus is a harmless condition.

Summary.

There appear to be at least two main subdivisions of oral epithelial naevi, one keratotic and the other parakeratotic. A case is reported of the type featuring parakeratosis and it is discussed in the light of cases recently reported under the title of familial white folded gingivostomatosis.

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ERYTHEMA NODOSUM.

A Study of Seventy Cases.

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Erythema nodosum should especially interest British physicians, for it was first described by Willan in 1798. In 1842, twenty years before Hebra's classical account, Erasmus Wilson drew its clinical features accurately in these words: "an inflammation of the skin occurring in oval patches, which vary in size, from a few lines to two to three inches in diameter, and are situated for the most part on the upper and lower extremities. The oval patches are slightly raised above the surrounding surface, the elevation increasing gradually towards the centre; they are hot and painful; of a bright red colour at their eruption; but change in the course of a few days to a purplish and livid tint, which becomes subsequently yellow and greenish and has the appearance of an ordinary bruise." Little has been added to the clinical description of the disease, but there has been constant speculation about its cause.

In the brief historical outline that follows we shall refer only to a few outstanding landmarks. Though erythema nodosum, or an eruption very similar to it, had been noticed in connection with syphilis and with drugs such as iodides and antipyrin, most British authors associated it chiefly with "rheumatism". This theory has persisted until the present day, despite overwhelming evidence against it.

Lendon, in 1905, suggested that it was a specific infectious disease, because several of his 63 cases had occurred in family groups. He also remarked on the frequency of phlyctenulae and the prevalence and severity of prodromal symptoms, among which were the articular pains that invited confusion with acute rheumatism. In the early years of this century, tuberculosis was becoming recognized as a sequel (though not yet as a cause) of erythema nodosum in young people and was regarded as a bad omen prognostically. Out of Lendon's 34 families, 5 had admitted an original or family history of phthisis and the only two patients who died did so of this disease. In 1907, Landouzy demonstrated satisfactorily and conclusively the connection between erythema nodosum and tuberculosis, but support for this view grew slowly. In 1912, Parkes Weber described the association as "occasional". By 1924 he was able to report "several cases" of it. The development of radiological facilities and the widespread use of the intradermal tuberculin test showed it more clearly. As a result, the aetiology was explored carefully but the original criteria for the diagnosis were not always closely followed. The earlier dermatologists were

in no doubt about its characteristics—" light-red nodules, either round-topped or oval in shape—tender to the touch, and mainly situated on the legs . . . the smallest the size of a pea and the largest of a closed fist " (Hebra, 1860). We emphasize this because there exists a good deal of confusion about the diagnosis of nodules on the legs. Until recently, only two varieties were commonly recognized, viz., erythema nodosum and erythema induratum. Many other types of nodular eruptions occur and may be overlooked, especially if the diagnostic criteria become blurred. For example, the lesions of Behçet's syndrome, thrombophlebitis migrans, " nodular vasculitis ", Trichophyton *rubrum* infection and recurrent cellulitis can all resemble erythema nodosum, though careful examination and a knowledge of their natural history will distinguish them.

During the next twenty years the importance of tuberculosis was particularly emphasized by those working in chest centres (Lemming, 1935 ; Daniels, 1944 ; Gray, 1945 ; etc.). But many others, particularly in Anglo-Saxon countries, continued to emphasize the importance of streptococcal infection, whether " rheumatic " or not. Forman (1936) found it to be by far the most frequent cause in his adult cases, and this has been the belief of most British writers until recent times (Spink, 1937 ; Frankel, 1945). Doxiades (1949), however, reiterated the overwhelming importance of primary tuberculosis as a cause in children and this is generally accepted by all workers.

Such was the position until 1941, when King in America found bilateral hilar-gland enlargement in 111 of 141 radiographs of patients with erythema nodosum. The first observations in this country were made by Paul and Pohle (1941), who described this syndrome in 9 out of 52 patients, and by Kerley in 1942. Van Beek (1943), Löfgren (1946) and others have demonstrated that these enlarged hilar glands are in fact part of generalized sarcoidosis. The importance and frequency of sarcoidosis has received increasing attention by many British authors in recent years (Scadding, 1950 ; Geraint James *et al.*, 1956). Much of this material however, has been drawn from larger teaching hospitals and chest centres where the cases of sarcoidosis may be more common. It seems possible that this actiological factor may have been over-emphasized.

Other causes and mechanisms have been postulated. For instance, Wallgren (1935, 1938) thought that many cases were due to various " provocative " agents influencing pre-existing tuberculous infection. At one time sulphonamides were widely incriminated, but it is difficult to know how often the eruption was due to the drug and how often to the infection for which it was given ; or if all the cases could rightly be called erythema nodosum. Other unusual causes of this disease are well recognized but play little part in this country e.g., coccidioidomycosis, lymphogranuloma inguinale and secondary syphilis. Thus we are faced with three main causes of erythema nodosum viz., tuberculosis, streptococcal infection and sarcoidosis. Their relative inci-

dence in England at present has not been established. With the decline in tuberculosis, the apparent importance of sarcoidosis overshadows all other causes and cases due to streptococcal infection have received little attention. We thought it useful, therefore, to analyse 70 consecutive cases seen in our own and other departments in general hospital practice over a period of seven years.

Material.

The main material for this study consisted of all cases of erythema nodosum seen by us over a period of seven years in a small area of south-east England (Table I). This area comprizes most of Buckinghamshire (except for the north-east and south-east corners) and adjacent strips of Hertfordshire and Oxfordshire. The population served by the hospitals to which the cases were sent is approximately 275,000. One or other of us saw all 62 cases on several occasions. In addition, 8 cases were seen by one of us (D.S.W.) at St. Peter's Hospital, Chertsey during the same period.

Table I.—*Total seen.*

	Total.	Bucks. series.
Total	70	62
Source :		
Seen in out-patients	33	29
Seen at home	19	17
Referred by hospital colleagues	18	16
Sex :		
Male	16	16
Female	54	46
Of the five patients under 12 years old		
3 were male		
2 were female		
The adult female : male ratio was	4 : 1	3·4 : 1

Criteria.

We excluded all cases which did not conform to the original description. We believe that the condition is well-defined and seldom atypical. Recurrent attacks occur, but we distinguish between true recurrence after months or years and recrudescence during the course of the disease which often occurs when patients get up prematurely.

The eruption shows the following features. The nodules occur mainly on the front of the legs and thighs, sometimes on the arms, face and neck. They are multiple and tender. Their size varies but is greater on the legs than on the thighs, arms or face, where nodules 0·5 to 2 cm. in diameter are commonly seen. The duration of the attack is from three to eight weeks. A bruising colour occurs during fading.

Sclerotic, ulcerated or indurated lesions do not occur and lesions of erythema multiforme do not normally co-exist. Some of our patients showed small, profuse lesions on the face, neck and arms, but we regarded these as true

erythema nodosum. There were no oral lesions, no " iris " lesions and no bullae. Mixed types occur and Löfgren saw 5 such cases in his series of 178.

Finally, histological evidence of " vasculitis " is not a predominant feature.

Age Distribution.

The age distribution of our cases is shown in Fig. 1 compared with that of 100 cases reported by Johnson, Hanson & Good (1951). It is that of a community in which adult primary tuberculosis is uncommon. Löfgren (1950) has shown

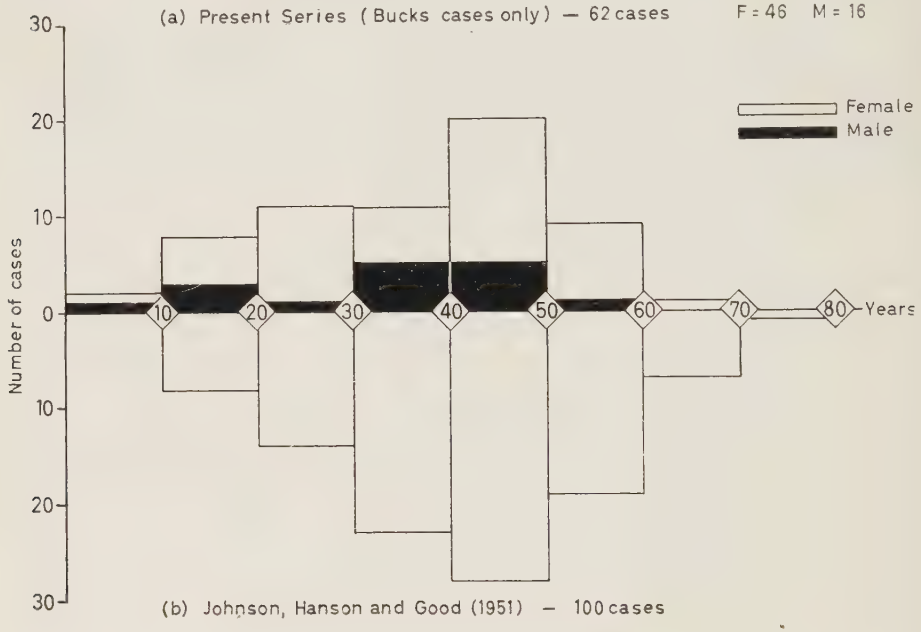

Fig. 1.

that the proportion of tuberculous cases diminishes rapidly with increasing age and Johnson, Hanson and Good pointed out that primary tuberculosis, with or without erythema nodosum, is very rare after forty years of age. There has therefore been a marked change in the age incidence of erythema nodosum with the decline of tuberculosis.

Analysis of Cases.

We arranged the cases in six main groups, according to the criteria given below. These groups are :

I Tuberculous.
II (a) Streptococcal (" proved ").
(b) Streptococcal (" presumed ").

III Bilateral hilar-gland syndrome without evidence of parenchymatous sarcoidosis.

IV Sarcoidosis.

V Middle-aged women with respiratory disease.

VI Miscellaneous and unknown.

87·2% of the cases fell into the first five groups and 12·8% (9 cases) were of mixed or undecided aetiology (Fig. 2).

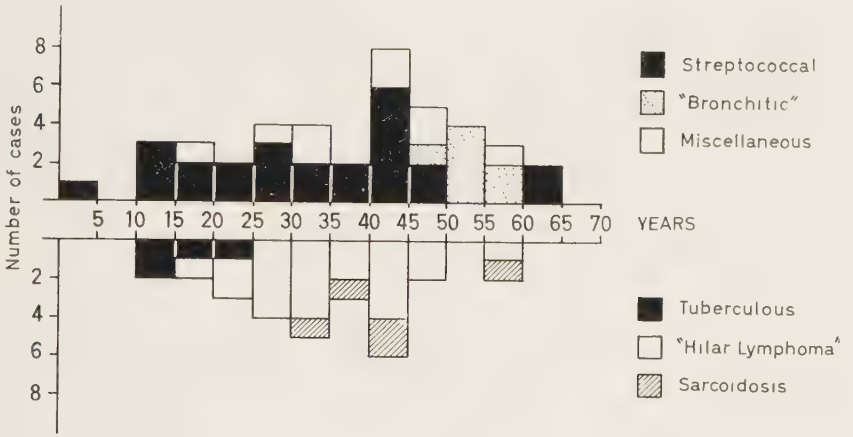

Fig. 2.

I. Tuberculous.

There were 4 cases, 2 male and 2 female. The diagnosis rested on the association of recent primary tuberculosis with erythema nodosum. Tuberculosis was confirmed by finding tubercle bacilli in the sputum in two cases, the presence of tuberculous cervical adenitis in one case and clear X-ray evidence of a primary tuberculous lesion in the fourth. The diagnosis is straightforward and must always be considered first in patients under the age of thirty but it may not become apparent for some months.

A girl of 19 developed erythema nodosum. The Mantoux reaction was positive in 1 : 1000 and bilateral hilar adenitis was present, predominantly on the right side. This adenitis subsided over a period of 9 months, when a further radiograph showed that she had developed typical pulmonary tuberculosis.

The oldest patient in this group was 24 years of age. We have not found tuberculosis to be an important cause, except in children and adults under 25.

II (a) Streptococcal (" Proved ").

There were 8 cases, 1 male and 7 female. These fulfilled the fairly strict criteria used by Forman (1936) viz., the finding of beta-haemolytic streptococci, with or without a raised anti-streptolysin titre (300 units or more). There was

usually preceding tonsillitis (5 cases) but other patients had had an acute upper respiratory infection, sore throats or carious teeth.

The eruption followed the infection by one to three weeks, except in one case, where it was synchronous with the patient's sore throat, other members of the family having had sore throats in the preceding weeks.

II (b) Streptococcal (" Presumed ").

There were 17 cases, 3 male and 14 female. We have included those cases in which beta-haemolytic streptococci were not recovered when the patient was seen, or culture was for some reason not carried out. The evidence of a streptococcal origin rested on a history of tonsillitis or other streptococcal infection within three weeks of onset, or a family history of presumed streptococcal infection, the exclusion of sulphonamides, antipyrin or iodides and the absence over a minimum period of seven months' observation of any radiological or other evidence of tuberculosis or sarcoidosis.

These two groups are taken together in the discussion of their clinical features.

Age distribution.—Four to 75 years. Main incidence 10 to 50. It was more common after 25, with a peak at 40 to 45. These findings are similar to those of Löfgren (1946).

Prodromal symptoms.—In half, joint pains and excessive fatigue occurred at the same time as tonsillitis. Other prodromal symptoms were not marked. The onset of the eruption was usually abrupt with pyrexia.

Course.—The patients showed a high sedimentation rate at the onset. The course was variable, being excessively prolonged in a quarter, in whom joint pain and fatigue persisted for up to 5 months. The eruption itself had usually subsided within three to four weeks but three patients had recurrent nodules three to four weeks after the onset. Two patients had second attacks eighteen months to three years later. Moderate polymorphonuclear leucocytosis occurred in half.

Previous treatment.—None had been treated with sulphonamides.

Radiological changes.—These were uncommon, but occurred in three patients with unilateral hilar adenitis in one and bilateral in two. All were in young people and the changes resolved within two months. These are recognized as occurring in streptococcal and other infections (Löfgren, 1946).

Other symptoms.—Phlyctenular conjunctivitis was seen in one patient. The tuberculin and Kveim reactions are discussed later.

This was the only group in which there were relatively more patients from urban than from rural areas.

III & IV " Bilateral Hilar-Lymphoma " and Sarcoid Groups.

Though we accept the view that the association of bilateral hilar-gland enlargement and erythema nodosum represents an early stage of sarcoidosis

and we have found evidence of this in some of our patients, there seemed to us to be enough differences in the clinical features and course to divide these patients into two groups. We have for convenience called the first group the "bilateral hilar-lymphoma syndrome". This is a clumsy and pathologically incorrect term but no satisfactory alternative exists. "Nodal fever" is in many respects better but has become identified with Lendon's idiopathic cases.

Bilateral Hilar-Lymphoma Syndrome.

There were 20 cases, 6 male and 14 female. The average age was 32 years, ranging from 18 to 44.

Prodromal symptoms.—Sixteen had marked prodromal symptoms. The remaining four had minimal prodromal symptoms and a mild course. Fatigue with joint pains predominated, loss of weight occurred in four patients, dyspnoea and cough in six, and two patients had severe diarrhoea and vomiting three weeks before onset of the nodules.

Course.—Five patients had recrudescent nodules over a period of four to five weeks, even though in bed. Two of the patients complaining of loss of weight and cough had a prolonged illness lasting 18 to 24 months and showed transient parenchymatous lesions. In a quarter of the patients the chest remained radiographically abnormal for over 18 months. In the remainder, the symptoms cleared and the chest reverted to normal in under 18 months, the majority taking more than a year to clear. This parallels the experience of other observers (Löfgren, 1953; Geraint James *et al.*, 1956).

Other symptoms.—Enlargement of the right supratrochlear glands developed in two patients. Iritis or conjunctivitis were present in four cases at the onset. Seven of the twenty were markedly depressed, frequently bursting into tears without provocation. The symptoms were severe enough for three patients to be admitted to a mental hospital. Such depression was not present in the remainder, though a certain amount of emotional lability occurred in those who had suffered from a prolonged prodromal period of fatigue and dyspnoea.

Tuberculin reaction.—None was positive to 1 : 10,000 Old Tuberculin, 8 showed positive reactions to 1 : 1,000, 5 to 1 : 100 only, 5 were negative to 1: 100 (4 of these reverted later) and 2 were not tested early in the disease.

Histological changes.—Of 8 biopsies performed, 5 showed a sarcoid reaction and 3 were non-specific. The Kveim reaction was positive in 4 patients.

Comment.—It has been explained that some cases in this group showed unmistakable signs of sarcoidosis elsewhere. Four patients developed skin sarcoidosis during the course of their disease, either in the sites of the nodes themselves or in scars which were long-standing or due to our biopsy. These lesions were relatively short-lived and disappeared at the time of the other symptoms. Of the intermediate cases the following is of interest.

A hospital registrar, a woman aged 29, had previously shown a Mantoux-positive reaction to 1 : 1000. She developed erythema nodosum and hilar gland enlargement, predominantly on the right side. The Mantoux reaction was positive to 1 : 100 only and negative to 1 : 1000. A biopsy of the node showed no specific changes until serial sections demonstrated one typical sarcoid nodule. She later developed right-sided cervical adenitis, sarcoid deposits in the eye and sarcoid changes in the biopsy scar. Her illness ran a course of 18 months before resolving completely without any evidence radiologically of parenchymal lesions. Her E.S.R. became normal in four months.

Erythema Nodosum with Pulmonary Sarcoidosis.

There were 5 cases, 4 female and 1 male. The average age was 42 years, ranging from 33 to 57.

Prodromal symptoms.—Fatigue and joint pains again predominated, but in addition cough, dyspnoea and loss of weight commonly occurred.

Course.—This was prolonged, continuing for three years so far in one case and for over 18 months in two others. The E.S.R. behaved at first like that of the preceding group, but in two cases rose again at the 8 to 10th week after onset and persisted at a high level for several months. The course was characterized by dyspnoea, cough and considerable disability. No deaths occurred but pulmonary changes in one case persist after three years. No recurrent attacks occurred in these two groups.

Histological changes.—Typical sarcoid lesions were found, from the tonsil in one case, the bronchus in another and the skin in the remaining three. A positive Kveim reaction occurred in the only patient tested.

V " Bronchitic " Group.

There were 7 cases, all female. Age range 48 to 54 years. This group seemed to us to be worth recording separately as its features invite confusion with sarcoidosis.

Prodromal symptoms.—Fatigue, joint pain, cough and dyspnoea were present in all cases, but no loss of weight had occurred. The patients were tired, restricted in their activities and had a history of recurrent attacks of respiratory infection over many years. No iodides had been taken in the form of cough medicine. One patient had had a five-day course of sulphonamides immediately before the eruption. All cases occurred in April, May or June and appeared to follow an exacerbation of chronic bronchitis.

Course.—The onset of erythema nodosum, which was typical, was abrupt and accompanied by general disturbance, with fever, fatigue, lassitude and cough. The patients looked and felt ill. Recrudescences of the eruption occurred in three while confined to bed. The cough and dyspnoea ameliorated very gradually and were not influenced by antibiotic or other therapy. In general, both the attack and the course were severe and disabling. The average E.S.R.

at the onset was 41 mm. in 1 hour. This remained raised in three cases for 1 to 3 years, but in the other four reverted to normal in 3 to 4 months.

Radiological changes.—All showed evidence of chronic bronchitis and emphysema; one showed lobar collapse which later re-expanded and another bilateral bronchopneumonia. In no case was there any evidence of pulmonary tuberculosis or sarcoidosis at the time or during a follow-up period of 1 to 3 years.

Comment.—In such a small series it would be unwise to attach particular significance to this group. We feel that it is distinctive enough to be recognized, if only for the purpose of separating it from that of sarcoidosis, which is common at the same age. Frankel (1945) described a group of severe cases of erythema nodosum in middle-aged women, which he regarded as streptococcal in origin. Johnson, Hanson & Good (1951) found a peak of cases, nearly all of streptococcal origin, in the 40–50 age group and it is clear that the association of erythema nodosum with streptococcal infection knows no age barriers. It has been shown (Brumfitt, *et al.*, 1957) that acute exacerbations of chronic bronchitis are not necessarily associated with a predominance of streptococcal pathogens in the throat or sputum. In two of our cases these organisms were cultured from throat and sputum, but no bronchial cultures were obtained.

Erythema nodosum is not associated with infections due to the pneumococcus or *H. influenzae*; whether it is due here to the streptococcus (which seems likely) or to other unknown causes, must remain open until there is further clarification of the normal and pathogenic flora in patients with chronic bronchitis.

VI Miscellaneous Group.

We included here nine cases which did not fit easily into the preceding groups.

(i) Sulphonamides with streptococcal infection	1
(ii) Sulphonamides with diarrhoea and vomiting	1
(iii) Diarrhoea and vomiting	2
(iv) Streptococcal infection and tuberculosis	2
(v) Aetiology not determined	3

(i) *Sulphonamides with streptococcal infection.*—This case fulfilled the criteria of a presumed streptococcal infection but had been treated with sulphamezathine at the onset of the sore throat. The subsequent erythema nodosum differed in no way from those included in the streptococcal group and it was considered unlikely that sulphonamides played any decisive part in the eruption. With the decline in the use of these drugs, the proportion of cases due to streptococcal infections alone remains high, but two other cases not included in this series demonstrate that an eruption very similar to erythema nodosum may occur in conjunction with sulphonamide therapy and without obvious streptococcal infection.

A course of sulphapyridine was recommended for a boy of 19 with cystic acne. He was given sulphathiazole instead. Within ten days he developed three erythematous

nodules on the thighs and legs. These subsided when the drug was discontinued. There was no elevation of the sedimentation rate and no bruising colour noticed on resolution, which occurred within a few days. A woman of 68 had a history of chronic diverticulitis. She was given a course of phthalylsulphathiazole prior to resection. A second course of this drug was given for six days after operation and was accompanied by a rise in temperature lasting a week. Thirteen days after this she produced erythematous lesions which faded in the course of a few days without bruising. Although a streptococcal infection cannot be excluded, the short-lived erythematous lesions were not wholly typical of erythema nodosum.

A further case in which sulphonamides were given is described below.

(ii) *Sulphonamides with diarrhoea and vomiting.*—This case was similar to the two described below, but had been given sulphathiazole two weeks before developing typical erythema nodosum. As the other two cases had not received the drugs, it seems unlikely that it played any part in causing the eruption.

(iii) *Diarrhoea and vomiting alone.*—Two cases presented with diarrhoea and vomiting of acute onset lasting only a few days. A week later the patients, a man of 30 years and a woman of 43, developed typical erythema nodosum. After prolonged observation there was no evidence of tuberculosis, streptococcal infection, enterocolitis or diverticulitis. No sulphonamides had been given. The erythrocyte sedimentation rate returned to normal in two and four months respectively. No pathogens were cultured from the stools.

We are unable to give any opinion about the "provocative" effect of sulphonamides. Sulphathiazole has always carried a particular stigma in this respect and in our few cases this compound has been associated with attacks.

(iv) *Streptococcal infection and tuberculosis.*—

A girl of 19 years had a septic toe for which she was given penicillin three weeks before the onset of erythema nodosum. She had lost a stone in weight over the previous six months and developed haematuria a week before the eruption. On admission she presented the clinical picture of pyelonephritis and erythema nodosum. Casts and albumin but no tubercle bacilli were found in the urine. Beta-haemolytic streptococci were grown from the throat. The Mantoux reaction was strongly positive in 1 · 10,000 dilution. Skin biopsy showed histiocytic foci resembling Aschoff nodes. She made an apparently complete recovery but was readmitted three months after the onset of her original illness and died within forty-eight hours. Post-mortem findings were those of subacute nephritis with miliary tuberculosis.

The association of streptococcal and tuberculous infections has been emphasized by Löfgren (1946) and Wallgren (1938). It seems likely that this girl had suffered a recent primary tuberculous infection which was exacerbated by a streptococcal infection.

We have seen a further case in which tuberculosis—this time of long standing—became active following streptococcal infection.

A man of 56 years with a calcified focus in the right upper lobe developed erythema nodosum following recurrent streptococcal infection amongst his family. Radiological evidence of activity of the tuberculous focus followed and took two months to resolve.

Discussion.

Age and sex.—The adult ratio of 3·4 female to 1 male in the Buckinghamshire group corresponds to that of Johnson, Hanson and Good (1951), but is less than in many other series. James (1956) found a ratio of 2·4 : 1 in his series of sarcoid cases and our rather low ratio may reflect the number of such cases included. But in 28 cases recorded in a preliminary general practitioner survey the predominence of females was also less marked and here streptococcal cases were the most frequent. In both series children of both sexes were equally affected.

The age span and average ages of each group have been given already. In general, tuberculous cases occur predominantly in childhood; streptococcal cases have a wide span from childhood to old age, predominantly from 25 to 50; the bilateral hilar-lymphoma syndrome occurs from late adolescence to 50 and generalized sarcoidosis was seen from 30 to 60. The "bronchitic" cases were confined to a narrow span of 48 to 54 years but would probably extend some way on either side of this in larger series.

Bruising.—We regard this as a characteristic feature of the disease. It was present in all cases. But we believe that it may be absent when erythema nodosum is an early feature of sarcoidosis and the lesions rapidly become infiltrated with cellular sarcoid deposits. These cases also persist and represent one of the varieties of the "*hypodermites nodulaires*" of French authors. It was absent in nodal eruptions following sulphonamide therapy and was not present in one case of a true nodal trichophytid complicating a severe case of *Trichophyton discoides* infection in a boy of 9, in whom bilateral single lesions on the shins lasted for only ten days. Bruising is not a characteristic feature in certain other conditions which may be confused with erythema nodosum, but which appear to consist essentially of vascular thrombosis with surrounding inflammation i.e. Behçet's disease, "nodular vasculitis" and thrombophlebitis migrans. In a series of 20 cases of "nodular vasculitis" studied by one of us (D.S.W.), none showed the typical bruising changes of erythema nodosum.

E.S.R.—The erythrocyte sedimentation rate is commonly recognized to be high in erythema nodosum. Löfgren (1953) found "very high" figures in 30% of his cases. This test was carried out repeatedly in the majority of our cases and whenever possible until it had returned to normal and remained so. The average figure (Wintrobe) at two weeks after onset was 36 mm. in 1 hour, with a range from 31 to 42 mm. There was little difference in the E.S.R. at the onset between cases of different aetiology. There are certain indications that a continued high E.S.R. or failure in a few cases to return to normal, is due to the presence of disease other than the erythema nodosum. The initial level bore a rough relationship to the severity of the erythema. Persistently

high levels were found in the " bronchitic " group but not in the uncomplicated streptococcal cases.

Of great interest to us was the different behaviour of the E.S.R. in the " hilar-lymphoma " groups, when a steady fall to normal took place in sixteen weeks, and the " sarcoid " group where, in all but one case, there was a second-

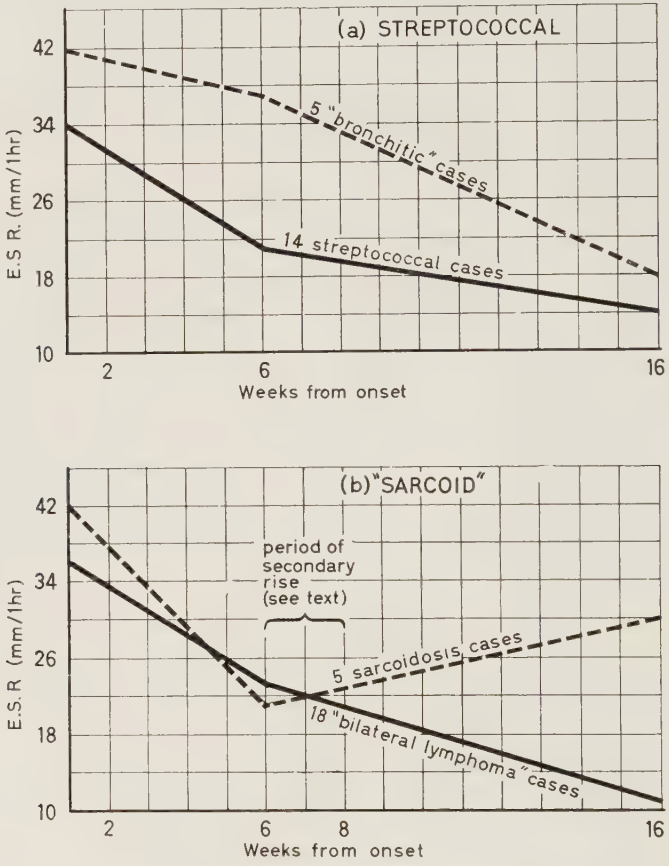

Fig. 3.

ary rise. In two cases this occurred between the sixth and eighth week after the onset ; in two no figure was obtained between the fifth and twentieth weeks, but the E.S.R. scarcely changed in that time. Such a rise can be taken to indicate spread or increase in the disease with parenchymatous involvement and to predict a prolonged course. The average slope of decline of the E.S.R. in different groups is shown in Fig. 3.

Tuberculin reaction. -We do not place overmuch reliance on the tuberculin reaction in sarcoidosis. The figures for conversion at different ages are not known but in the area from which the cases were drawn 23% are said to have

positive reactions at 13 years of age and (High Wycombe) 14·1% at 10 years. The rate at 30 years is regarded as virtually 100% (Hawkins, 1957).

Table II shows that roughly one-third of the sarcoid and hilar lymphoma cases were positive to 1 : 100 dilution only and one-third negative. Four of the five negative reactors had reverted within 2 years and one remained negative.

TABLE II.—*Mantoux Reaction in Erythema Nodosum.*

Type	1/10,000	1/1,000	1/100		Not done	History of Tb.	Tb. in family
	+	+	+	−			
Tuberculous	4	0	0	0	0	0	1
Streptococcal	1	5	1	0	1	0	1
Presumed streptococcal	1	7	3	1	5	0	0
Bilateral lymphoma	0	8	6	5*	1	1	0
Sarcoidosis	0	1	2	2†	0	1	0
" Bronchitic "	1	2	2	0	2	0	0

* 4 cases reverted to positive at the end of the disease : 1 remained persistently negative for two years.

† 1 reverted to 1/100 positive in 16 months.

Candida skin tests were not carried out routinely in this series, but reports and our observation on recent cases suggests that combined testing is of great value in confirming a diagnosis of sarcoidosis.

Prodromal and accompanying symptoms.—There is little to be added to the features already given. Few distinguishing symptoms occur, but loss of weight, otherwise unexplained, when associated with cough and dyspnoea, is very suggestive of sarcoidosis. This did not occur, though the other symptoms did, in the " bronchitic " group. Joint pains were common to all groups, but were not invariably present. They were absent for instance, in one-third of the streptococcal cases. We do not regard them as being in any way specific. We have noted the curious frequency of depressive states in the sarcoid groups. While depression is recognized as occurring in prolonged toxic states, we can find no reference to its association with sarcoidosis.

Recurrent attacks.—Four patients gave a clear history of recurrent attacks ; three belonged to the streptococcal group and one to the " undetermined ". The previous attack in these three had also followed sore throats or other presumed streptococcal infection. These four examples coincide with Löfgren's assertion that " in cases where there are several recurrences of erythema nodosum a non-tuberculous aetiology is in question ".

The comparison of some of the features in the main groups of cases is shown in Table III.

Histology.—The histology will not be discussed in this article except to mention that the non-specific changes described by Löfgren and Wahlgren (1949) were found in most lesions, though typical sarcoid changes occurred in 2 out of 6 cases examined in the " hilar-lymphoma " group.

TABLE III.—*Comparison of Some Features in the Main Groups of Erythema Nodosum.*

Group.	Cases.	Average age and span.	Prodomal symptoms.	Severity of attack.			Other areas affected.		Duration of symptoms.*
				Severe.	Mod.	Mild.	Arms.	Face & neck.	
Streptococcal	8	43·7 (26–63 years)	5	1	3	4	1	1	2 to 5 months.
Presumed streptococcal	17	30·3 (4–73 years)	9	3	6	8	3	4	1 to 5 months.
Bilateral lymphoma	20	32·2 (18–44 years)	15	3	10	7	6	6	Over 6 months.
Sarcoidosis	5	42·6 (33–57 years)	5	2	2	1	2	1	7 to over 24 months.
Bronchitic	7	53·1 (48–56 years)	7	3	4	0	2	3	3 to 4 months.

* From onset of preceding illness or of first prodromal symptoms to loss of all symptoms.

Kveim reaction.—Professor Neils Danbolt kindly gave us a supply of Kveim reagin which enabled us to carry out this test in 6 of our cases of erythema nodosum as well as in 8 controls and 4 sarcoid cases. No positive reactions were obtained in the controls but all the sarcoid cases showed positive results. Of the 5 cases tested in the hilar-lymphoma group, 4 showed a positive reaction on histological examination and in one, no nodule or reaction was found on excision of the area. This was probably because of a failure in technique in the early stages. Only one Kveim reaction was carried out in the streptococcal group and this was negative.

James (1956) obtained 80% positive reactions in his 24 patients with sarcoidosis and erythema nodosum. If enough material were available its routine use in all cases of erythema nodosum of doubtful origin would be a very helpful aid to diagnosis.

Radiological changes.—Bilateral hilar adenitis was found consistently in the hilar-lymphoma and sarcoid groups. In the latter, this was associated in all cases with parenchymatous changes, which have persisted. In two patients of the hilar-lymphoma group there were transient parenchymatous lesions. In the majority of these cases the hilar adenitis persisted for six months to two years, but the patient was always clinically well and the E.S.R. normal before this occurred.

Two cases of streptococcal origin showed bilateral hilar adenitis. One of these was in a child of four. No radiological or clinical evidence of tuberculosis or sarcoid was found. The hilar shadows subsided within two months, before clinical recovery occurred or the E.S.R. was normal. One patient had unilateral adenopathy, the significance of which has been referred to previously.

Comparison of the prognosis of sarcoidosis and the hilar-lymphoma syndrome.—Scadding (1950) uses the term "sarcoidosis" to denote "that group of cases

in which there are generalized changes having a similar histology to that of the skin lesions which the dermatologists have named sarcoids ". This histology, however, is also familiar to dermatologists in silica and beryllium granulomas and may even occur in typical lupus vulgaris. Geraint James *et al.* (1956) found histological evidence of sarcoidosis in 27 patients with the syndrome of erythema nodosum and bilateral hilar-gland enlargement with or without parenchymatous lesions. In 13 cases this evidence was from skin, liver or glands and in 2 cases from the erythema nodosum lesion itself. In 1953 Löfgren had studied 212 patients with " large bilateral hilar lymphomas with negative or weakly positive tuberculin reaction " ; 113 (i.e. half) of these cases presented with erythema nodosum and in 70 other cases the condition was found radiologically with few or no symptoms. Of his 113 cases with erythema nodosum, 9% showed parenchymal lesions at the onset and 28% developed these later. Anderson (1957) found that 20% of his cases of erythema nodosum with hilar adenopathy showed parenchymatous changes at the onset and that another 20% developed these within a year. Of Löfgren's cases of hilar adenopathy without parenchymatous lesions, 48% resolved within a year and 90% within two years ; 80% of Anderson's cases which developed parenchymatous changes later in the disease showed such changes for more than two years.

Patients who showed erythema nodosum seemed to Löfgren to have a better prognosis and this was also stressed by Scadding and by Geraint James. Only one of Löfgren's cases showed lesions elsewhere than in lymph nodes and lungs. In those who developed lesions on the skin, one half did so in scar tissue, either at the onset or subsequently. In our cases we found sarcoid changes elsewhere in five patients. We have already pointed out that a drop in the E.S.R. seems to precede and to presage resolution and that the Mantoux reaction may revert at about the same time. The Kveim test is said (Nelson, 1949) to be negative in resolving or resolved cases.

TABLE IV.—*Bilateral Hilar-Lymphoma (B.H.L.) and Sarcoid Groups.*

(a) *Duration of hilar-gland enlargement.*

	Resolved within		
	1 year.	18 months.	2 years.
Without parenchymatous changes	4	9	5
With transient parenchymatous changes	0	0	2
With lasting parenchymatous changes (" sarcoid " group)	0	2	2 (and 1 over 2 years)

(b) *Other organs affected.*

	B.H.L. (20 cases).	Sarcoid (5 cases).
Eyes	4	3
Skin (scars)	4	3
Lymph glands (not hilar)	2	2
Other : Joint effusion	1	-
(Mental disturbance)	7	-
Total patients	8	3

Conclusions.

1. Seventy consecutive cases of erythema nodosum have been analysed. Sixty-two of these were seen over a period of seven years in an area of south-east England with a population of 275,000.

2. The criteria for the diagnosis of the different aetiological groups are given and the features of the cases in each group are presented. Of our cases, 45·6% were of proven or presumptive streptococcal origin, 5·6% were tuberculous, 35·7% accompanied sarcoidosis and 13% were of mixed or unknown origin.

3. Reasons are given for separating those cases showing only or predominantly hilar-gland enlargement from those showing more generalized changes of sarcoidosis.

4. The significance of certain clinical features and of the behaviour of the erythrocyte sedimentation rate is discussed.

5. The results and value of the Kveim reaction are presented and commented upon.

6. A group is described of middle-aged women with erythema nodosum following an exacerbation of chronic bronchitis with severe toxic symptoms.

7. The frequency of depression in cases of sarcoid type is mentioned.

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LETTER FROM MUNICH.

Munich is at the end of a long straight Autobahn which runs due south from Cologne and is the capital of Bavaria. The last monarch, King Ludwig III, reigned from 1913 until the republic was formed after the first world war. There is a nostalgia for the old monarchy. The Kings of Bavaria were dearly loved and the castles and historic buildings of the old kingdom have been carefully preserved. The scars of war have largely been replaced by modern twentieth-century buildings, which look a little embarrassed next to their Baroque, Rococo, and Gothic neighbours. The surrounding farmland is rich and food is a little cheaper than elsewhere in Germany. Housing remains a universal problem and the whole town vibrates with the building which is going on all around.

Fig. 1.

A hospital has existed in Munich since the early fourteenth century, but it was not until 1809 that Häberl founded the university clinic. It was situated near the Sendlinger Gate of the old walled city. This gate still stands and is only a short distance along the Lindwurm-strasse from the present building. Josef Lindwurm became Professor of Dermatology and Syphilology in 1859. He was a man of wide interests and he studied in Heidelberg, Paris and Vienna. He visited the British Isles, worked under William Stokes and wrote a paper on " Typhus in Ireland ". He was followed by Posselt, Kopp and von Zumbusch.

The large building of the " Hautklinik " consists of an outpatient department with laboratories, consulting rooms and a fine library (Fig. 1); this is connected by a covered passage to the inpatient hospital (Fig. 2), which is at present shared with the surgeons. The ground floor hall is divided into male and female sections. The segregation of the sexes is understood when it is remembered that venereology is also practised in the clinic and forms approximately 5% of the work. There is no appointment system and patients are seen during the mornings only. Two or three assistants see both new and old patients under the supervision of an " Oberarzt " or senior registrar. In all cases the prescriptions are made up by the pharmacist of the patient's

choice, for there is no hospital pharmacy. The cost of drugs is met by the insurance scheme to which the patient belongs.

From his rooms above the outpatient department, Professor Alfred Marchionini (Fig. 3) directs his huge clinic and edits the *Hautarzt*. He is assisted by Professor Hans Götz (Fig. 4) who is second in command of the unit. With the clinical assistants, research workers and foreign visitors, there are between thirty and forty doctors in the dermatological clinic. This is the only university skin department in Munich and cases are referred here from all over Bavaria. The population served is approximately nine million. The assistants work either in the outpatient departments or on the wards. Since there are 230 beds and an annual outpatient attendance of over 12,000 new cases, such specialization is inevitable. A great deal of trouble is taken to ensure that all the assistants see all the interesting cases. Professor Marchionini " visits " his patients weekly, seeing the male and female patients on different days. I used inverted commas for " visits ", since the patients really visit the Professor.

Fig. 2.

There are too many assistants to make a ward round and so the doctors sit in a horseshoe in a side room with the Professor at the apex and the patients are presented by the doctor in charge of the case. His concise summary of the history and treatment is facilitated by a chart which not only shows the temperature etc., but also clearly shows the internal and external medication. The whole team meets at noon each day when interesting outpatients are presented in a similar manner. All the German doctors I have met have great clinical fluency and are able to recite the history, present state and progress without a moment's hesitation.

In order to explain the teaching of dermatology in Munich it is necessary to consider the general plan of undergraduate teaching in medicine. The medical student is taught in an academic atmosphere and the main bulk of teaching consists of lectures. There are practical lessons in anatomy, physiology, histology, bacteriology, etc., when work is done in the dissecting room or laboratory. However, the greater part of the students' time from the commencement of studies to the final state examination is spent listening to lectures.

There are two semesters in a year and together they occupy seven months. The other five months of the year are " vacations ", during which the students pursue private studies. The first five semesters are devoted to preclinical studies, after which the student takes up clinical subjects for the remaining six. For the whole time he attends a full programme of formal organized teaching. The various specialized departments (e.g. obstetrics, surgery, internal medicine, paediatrics, dermatology), occupy separate buildings in the " medical clinic area " of the town. Each clinic is directed by a professor and each has its own wards, outpatient departments, lecture

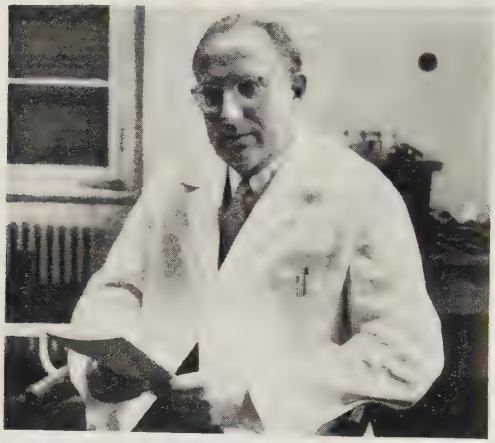

FIG. 3.

FIG. 4.

theatres and a full complement of teaching staff. Following his timetable, the student moves from clinic to clinic receiving his lectures from the appropriate professor.

Time is set aside for the study of sick patients in hospital. During the vacations he is required to spend six months as an unqualified assistant or medical clerk on the wards. He must also spend six months in the wards of the obstetric unit. His main experience of bedside medicine is gained during the two years which he is required to spend as a medical assistant after qualification. He may not practise until this period has been served. These two years must be spent as follows : 4 months in the surgical clinic, 4 months in the obstetric clinic, and 6 months in the department of internal medicine. The medical assistant may spend the remaining 10 months in the clinics of his choice. The place of dermatology within this structure is impressive and in the battle for the students' attention, this speciality has done very well in Germany. Students receive dermatological teaching during two semesters. They receive three one-hour lectures weekly from Professor Marchionini (compulsory) and two one-hour lectures from Professor Götz. There are further voluntary courses given by the Dozents (Readers). This scheme ensures that the students receive a minimum of approximately 100 hours of organized teaching in dermatology.

Professor Marchionini delivers a course of lectures which cover each subject thoroughly. He often shows relevant ward patients during his lectures. Professor Götz gives a series of more practical lectures. He selects six or seven typical cases which presented that morning and shows them to the students in the large lecture theatre, giving a short talk on each. In this way the students are shown a cross-section of the patients attending the outpatient department. These lectures are unprepared and are stimulating discussions of whatever cases happen to come along. The large number of beds, and the large number of outpatients ensure that there is no shortage of clinical material.

During the ten months' period when the medical assistant may choose his subject, some of them elect to spend three or more months in the dermatological clinic. It is noteworthy that dermatology is one of the subjects in the final examination and no candidate can be successful unless he satisfies the professors of dermatology. I believe that this is the deciding factor in making the newly qualified German doctor more conversant with common skin disorders than his British colleague.

Professor Götz has done a great deal of research on the pathogenicity of the dermatophytes. His interests are wide and he has published work on the treatment of skin disorders with penicillin, the aetiology of acrodermatitis atrophicans (Herxheimer), as well as numerous other subjects. He has suggested a method of treating tinea unguium and has clarified the problem of the mosaic fungus.

There is a mycological laboratory where an assistant takes specimens, searches for fungi and sets up cultures.

The physiology of the skin is the main interest of Professor Spier, who left Munich last October to occupy the chair of dermatology in Berlin. He did a great deal of work with Frau Dr. G. Pascher, who is in charge of the biochemistry department. They have worked extensively on the surface pH of the skin and the free amino acids, lactic acid, chloride, potassium and sodium content of the epidermis.

Dr. Meinicke is head of the serological laboratory where routine investigations are carried out and a lot of research is done. He has written papers on the culture of spirochaetes on artificial media, the pathogenicity of spirochaetes and the evaluation of serological reactions, and has studied many dermatological diseases from a serological standpoint. Virology in dermatology has been the subject of research pursued by Dr. Nasemann. His earlier papers suggested the value of electron microscopy in the investigation of dermatological disorders and he has gone on to publish interesting work on molluscum contagiosum, common warts, herpes simplex, etc. Work on the recent epidemic of " erythema infectiosum " is about to be published.

For the last five years, soft irradiation has been used in the radiotherapy department and Dr. Schirren who is in charge has had considerable experience with the

Dermopan apparatus, using qualities emitted between 12 and 50 Kv. He shows visitors the old conventional X-ray machine, the Chaoul, Grenz-ray apparatus, as a guide might indicate the old cannon in the Tower of London. His department now thinks in terms of tissue half value layer, and an effort is made to give the minimum effective dose of the quality which reaches the required depth but penetrates no deeper than necessary. When used at two metres distance with 50 Kv unfiltered, the Dermopan gives a quality at the skin surface of tissue H.V.L. less than 2 mm. (skin), because of air filtration. This method (Fernbestrahlung) is used to treat mycosis fungoides as well as persistent benign erythrodermas.

In general, I have been surprized to find how young the specialized research workers are ; many are authorities in their special branches. This is the outcome of the tendency to specialize within the specialty in clinics of this size. The more senior of these workers are now engaged in preparing their contributions to the new edition of Jadassohn's *Handbuch*, which is being edited by Professor Marchionini. The first volume of this monumental work will be available later on this year.

Frau Dr. Schumachers is especially keen on cosmetic dermatology. She not only removes excrescences most beautifully, but tackles wrinkles as well. For dermabrasion she uses the high speed motor designed by Schreus, which renders solid freezing of the skin no longer necessary. Anaesthesia is produced by novocain infiltration. She has a small " salon " and is aided by a cosmetician who attends the outpatient department. Dr. Röckl is in charge of female outpatients and of the bacteriological laboratory. He has published work on both clinical and bacteriological subjects. Dr. Borelli is in charge of the male out-patient department and has written a book on the psychosomatic aspects of dermatology. On the whole, the workers in Munich do not seem to consider psychiatric factors of great importance.

Dermatological therapy differs here in several respects. Since the number of beds available is large, there is no difficulty in admitting to the wards disabling cases of seborrhoeic dermatitis, contact dermatitis and leg ulcers. Far more cases of severe tinea pedis attend here than at home. It may be said that the dermatomycoses produce one of the major problems in Munich. Dyes such as Castallani's paint and methylene blue are used much more frequently than in England and are used throughout the management of the case. The orderly progression from lotions, through emulsions, creams and pastes to ointments is not so often pursued. Fever therapy in indolent eczema and persistent urticaria is quite often used. Focal sepsis is vigorously excluded, so that even cases of acne vulgaris, when resistant to other measures, often undergo tonsillectomy, Crude tar is used " neat " in the treatment of chronic psoriasis and atopic eczema and I have not seen follicular irritation follow it. Topical therapy is on the whole much more heroic than I have seen elsewhere and preparations containing 20% sulphur, 10% Ichthyol and 20% Liq. Pic. Detergens are in everyday use. Of considerable interest is the treatment of chronic discoid lupus erythematosus by the local infiltration of persistent lesions with chloroquine solution. Good results follow in carefully chosen cases. Professor Marchionini is interested in the influence of climate on skin diseases and sends selected cases of atopic eczema to high mountain resorts for a " Klima Kur ". This results in an improvement which is maintained for a variable period after high altitude residence. In some cases a long remission ensues.

Although the terms of address used between colleagues sound rather formal to British ears—" Herr Kollege X ", or " Herr Oberarzt X "—there is a feeling of fellowship throughout, and the whole clinic meets for most excellent parties whenever an excuse arises.

Maurice Garretts.

Radcliffe Crocker Travelling Scholar,
1958–59.

CURRENT LITERATURE.

ON THE PREPARATION OF AUTOGENOUS STAPHYLOCOCCAL VACCINE AND ITS THERAPEUTIC USE. G. Mildschlag and S. Ortel. (1958) *Derm. Wschr.*, **137**, 658.

In view of the increasing use of antibiotics in chronic pyodermias, often with very poor results, the value of autogenous vaccines is stressed once more and their preparation described.

W. G. T.

ACRODERMATITIS CHRONICA ATROPHICANS (PICK-HERXHEIMER) AND ACROOSTEOLYSIS. G. Raschke. (1958) *Derm. Wschr.*, **137**, 217.

In two cases of acrodermatitis chronica atrophicans radiological abnormalities of the terminal phalanges of some toes were found consisting mostly in an absence of the distal expansion. In one case this manifestation can be explained on the basis of concomitant vascular disturbances; in the other it appears to be caused by neuro-vascular disturbances which are part of the acrodermatitis. It is felt that these changes will be found more frequently if X-rays of toes and fingers are taken as a routine in this disease. W. G. T.

DERMATITIS DUE TO WASHING AGENTS. K. A. v. Zezschwitz. (1958) *Derm. Wschr.*, **137**, 249.

Synthetic substances of complicated chemical nature have more and more displaced soap as a washing agent. The chemical structures of three different types of synthetic washing agents are given. Dermatitis caused by these substances is a summation of various factors such as alkalinity, defatting of the skin, denaturing of the skin proteins and roughening of the skin. Three clinical pictures are recognized, acute contact dermatitis affecting hands, arms, neck and face, chronic recurring dermatitis affecting the dorsa of the hands and an exanthematous form found mainly on the trunk and resulting usually from ineffective rinsing of garments.

The condition is found mainly in housewives and laundry workers. In a series of 378 cases of eczema in women 15% were due to washing agents. The maximum incidence was between the ages of 40 and 50.

Patients suffering from neurodermatitis and ichthyotics appear to be prone to dermatitis due to washing agents, which seem to be better tolerated in summer when sweat exercises some buffer action. Hardness of water is an additional factor in producing dermatitis.

Skin tests with concentrations over 1% produced a large percentage of reactors both in patients and controls, whereas 1% test solutions produced far more positive results in patients than in controls.

In view of reports of combined chromic acid and washing agent sensitivities, patients and controls were tested with $\frac{1}{2}$% chromic acid solution but the results showed no significant difference.

W. G. T.

PSORIASIS VULGARIS AND PARENCHYMATOUS LIVER DISEASE. H. Gertler. (1958) *Derm. Wschr.*, **137**, 329.

Evidence of disturbed liver function in cases of psoriasis has been produced on a number of occasions.

The author reports a case in which a patient who had suffered from liver disease since the age of 17 developed psoriasis at the age of 57. Though other authors have reported improvement of manifestations of psoriasis when jaundice developed, this patient showed a definite relation between the improvement of liver and skin conditions. W. G. T.

BROMODERMA TUBEROSUM. K. Leibl. (1958) *Derm. Wschr.*, **137**, 681.

The present rarity of bromine eruptions justifies the report of a case of bromoderma tuberosum. The condition is probably an allergic one, though skin tests are sometimes negative and non-specific stimuli may produce typical lesions. Bromoderma has been reported at the site of tuberculin and trichophytin injections, insulin injections, at sites where lesions of molluscum contagiosum had been removed by curettage and on the tongue of an epileptic. The histology of arteriolar

damage with surrounding necrosis, collagen necrosis in the neighbourhood of fat tissue and abscesses consisting of eosinophils covered by epithelial proliferation is in keeping with this allergic aetiology. W. G. T.

ON THE PRESENCE OF AN ACID GLYCOPROTEIN IN THE SCALES OF PSORIASIS. G. Weber and O. Braun-Falco. (1958) *Derm. Wschr.*, **138**, 789.

By special treatment of scales from psoriatic patients a new acid mucopolysaccharide bound to protein was isolated. This substance was not found in shavings from callus treated in the same way, though its presence in scales from an erythrodermic reticulosis suggests that it is not peculiar to psoriasis. The source of this substance is to be found either in the intercellular spaces of the epidermis or the non-keratinized cells themselves. W. G. T.

ON LACTIC ACID DEHYDROGENASE ACTIVITY IN BLOOD AND BLISTER FLUIDS. G. Weber and I. Wildner. (1958) *Derm. Wschr.*, **137**, 767.

The authors refer to other papers showing the presence of this enzyme of the glycolytic chain in human skin.

The blood serum of patients suffering from a variety of dermatoses showed no increased enzyme activity but cantharides blisters as well as spontaneous blisters showed greatly increased values. Contrary to previous observations it was not found that destruction of tissue rich in the enzyme results in an increase of its blood level. The failure of the enzyme to enter the blood stream is not yet explained, but it is considered that lactic acid hydrogenase is of importance in the mechanism of blister formation. In pemphigus vulgaris there was some correlation between enzyme activity and the severity of the disease. W. G. T.

CLINICAL VARIETIES OF PUSTULAR PSORIASIS. H. J. Schuppener. (1958) *Derm. Wschr.*, **138**, 841.

Until 30 years ago all cases of pustular psoriasis were classified either as acrodermatitis continua Hallopeau or impetigo herpetiformis Hebra. Even to-day some deny the existence of this disease whereas others wish to separate the picture from psoriasis. The author considers that there is a gradation according to the degree of exudation from psoriasis inveterata via psoriasis vulgaris and pustular psoriasis to the most severe and sometimes fatal cases of pustular psoriasis of the Zumbusch type which present bullous epidermolysis. The author differentiates his benign form of pustular psoriasis from the malignant Zumbusch type which always presents constitutional symptoms.

In the benign form there may be pustules inside one or other lesion and there may be acute exacerbations of existing psoriasis with pustules in the lesions; a pustular exanthem; or flexural lesions may temporarily present marginal pustules which later develop into typical psoriasis papules. Sometimes pustular lesions are the result of local applications. Acute intercurrent infections may also produce pustular lesions in previously typical psoriasis vulgaris.

According to Kogoj the argument that these lesions are pyodermic can easily be disposed of by histological examination.

The author recognizes three stages in the Zumbusch type: febrile exanthematous eruption, recurring pustular eruption with pyrexia and the most severe form with continuous fever, erythrodermia and cachexia.

The presence of mucosal lesions is stressed and the occurrence of scarring is not at variance with a diagnosis of psoriasis.

The absence of ocular manifestations and urethritis allows the exclusion of Reiter's disease as a diagnosis.

Contributory factors for development of pustular psoriasis may be the menopause, cardiac failure, concussion, allergy, diabetes and arthritic diathesis. The trigger mechanism may have been provided in the author's cases by nervous exhaustion, drugs, sunlight and intercurrent infections. W. G. T.

ON THE ACTIVITY THAT SOME DERMATOPHYTES EXERT ON THE TYROSINE/TYROSINASE COMPLEX. P. Pinetti. (1958) *Giorn. ital. Derm.*, **99**, 1.

The author shows that the inhibition of the tyrosine/tyrosinase reaction by *Microsporum audouinii*, which had been attributed to the production of a tyrosinase inhibitor by Robinson *et al.* (1953) *A.M.A. Arch. Derm.*, **68**, 428, is in fact because the fungus uses tyrosine. Other dermatophytes can do the same. A. L.

THE POTENTIALITIES OF THE POLARIZED LIGHT MICROSCOPE IN STUDYING THE STRUCTURE OF HUMAN SKIN. V. A. Puccinelli. (1958) *Giorn. ital. Derm.*, **99**, 9.

A discursive paper that touches on the appearances under the polarized light microscope of the horny layer, hair, epidermis and collagen and throws in some electron microscope studies for good measure. Three points of interest emerge : (1) In whatever way the horny layer is broken down the end-product consists of " elementary horny lamellae " which have a diameter of around 60 μ and a thickess of 100 Ångstrom units. (2) There are apparent extensions of collagen fibres into the epidermis. (3) Polarized light microscopy has possibilities for investigating alterations of the collagen. A. L.

CUTANEOUS AMOEBIASIS. A CLINICAL AND MORBID ANATOMICAL CONTRIBUTION G. Pozzo and R. Rabotti. (1958) *Giorn. ital. Derm.*, **99**, 40.

A man had peri-anal warty lesions which resisted destructive measures and eventually grew exuberantly to affect his penis and other sites. This phase of the illness lasted some years and passed into a terminal stage of destructive ulceration in which his nose and face were eaten away. The diagnosis was made shortly before death by finding *Entamoeba histolytica* in preparations of fresh tissue. Anti-amoebic treatment unfortunately failed to save him. At necropsy many amoebae were demonstrated in skin sections which also showed much pseudo-epitheliomatous hyperplasia. There was no gut infection.

Cutaneous amoebiasis is fully discussed in relation to this case which is said to be an example of the rare true amoebiasis of the skin, as distinct from the commoner eruptions which depend upon an extra-cutaneous focus of amoebic infection. The authors suggest that a breakdown of the immunity mechanism caused the final ghastly scene, but some of the illustrations of the histopathology suggest to me the possibility of a truly epitheliomatous hyperplasia.

A. L.

THE TREATMENT OF PRURITIS ANI BY A COMBINATION OF DEEP X-RAY AND (HYDRO)-CORTISONE OINTMENT. A. Giordano. (1958) *Giorn. ital. Derm.*, **99**, 75.

The author finds the combination more effective than simple irradiation. A. L.

IMMUNO-BIOLOGICAL RESEARCHES ON THE COLLAGEN DISEASES WITH SPECIAL REFERENCE TO LUPUS ERYTHEMATOSUS. IV.—THE OCCURRENCE AND SIGNIFICANCE OF CRYOGLOBULINAEMIA. L. Rasponi. (1958) *Giorn. ital. Derm.*, **99**, 113.

All 7 cases of disseminated L.E. examined had cryoglobulinaemia as compared with 1 out of 22 cases of discoid L.E., 1 out of 2 cases of generalized scleroderma and 0 out of 4 cases of localized scleroderma. The cryoglobulins behaved electrophoretically like gamma globulin and when purified and used in a complement deviation test for syphilis gave a positive result.

A. L.

ECZEMATID-LIKE PURPURA. M. Binazzi and A. F. Finzi. (1958) *Giorn. ital. Derm.*, **99**, 127.

A father (68) and son (45) simultaneously suffered from that kind of purpuric eruption whose name is a matter of controversy and would vary from clinic to clinic. The authors, who have chosen Doucas and Kapetanakis as godfathers, blame bacterial products derived from teeth and tonsils but do not mention having enquired about drugs, even though both patients were constipated and may have shared their patent medicines as well as the roof. The spots were suppressed by steroids but not by antibiotics. A. L.

THE SERUM PROTEIN PICTURE IN PELLAGRA. F. Allegra and M. Iori. (1958) *Giorn. ital. Derm.*, **99**, 156.

Serum protein, especially albumen, was deficient with the exception of gamma globulin. Treatment partially reversed the abnormalities. A. L.

OCCUPATIONAL CANCER. M. W. Goldblatt. (1958) *Practitioner*, **151**, 181.

Occupational carcinogens may be absorbed by any of the available routes. Carcinogenic aromatic amines being lipoid-soluble penetrate the skin before being metabolized. The metabolic process entails liberation of energy which is taken up by the germinal layer of the skin until a critical level is reached, at which some of the cells become malignant. Possibly small amounts

of radiation or chemical energy may render a cell more susceptible to endogenous completion of the carcinogenic process. Among the carcinogens discussed are radioactive paints, asbestos, haematite, nickel, " isopropyl oil " and chromium, as well as aromatic amines causing carcinoma of the bladder.

Pitch, tar, soot and mineral oils contain carcinogens. Two compounds that produce epitheliomata in mice have been demonstrated in catalytically cracked petroleum. R. J. C.

THE PROBLEM OF INDUSTRIAL DERMATITIS. F. F. Hellier. (1958) *Practitioner*, **164**, 181.

The difficulties in persuading employers to provide protective clothing and barrier creams are discussed. Except where there is true allergic sensitivity a change in occupation should not be advised. It is better for a man to continue his own job with minor modifications designed to diminish the amount of exposure to irritants.

Often there is a predisposing eczematous tendency, such as xeroderma, or a strong family history of eczema. Successful management depends on the assessment of constitutional, nervous, as well as environmental factors. R. J. C.

FOOD ALLERGY IN CHILDREN WITH ASTHMA AND ECZEMA. V. Lehmus and K. Roine. (1958) *Acta Allergol*, **12**, 186.

Intracutaneous tests with various foods were made on 1076 children, 404 with asthma, 539 with eczema, and 133 with both. Twenty-six children gave positive reactions to almost every food tested and 899 gave positive reactions to one or more foods. The number of positive skin reactions diminished with increasing age. In 17% of cases food allergy was considered important and these children were hyposensitized, most of them to milk. H. T. H. W.

HEPARIN AND HISTAMINE IN CANINE MASTOCYTOMA. G. Bloom, B. Larsson and B. Aberg. (1958) *Acta Allergol*, **12**, 199.

Mast cell tumours are common in dogs, particularly boxers. The mast cells are rich in heparin and histamine. Administration of histamine liberators caused disintegration of mast cells and a rise in the histamine content of the peripheral blood. H. T. H. W.

BASOPHIL LEUCOCYTES IN URTICARIA, ASTHMA AND ATOPIC DERMATITIS. Hans Horsman. (1958) *Acta Allergol*, **12**, 205.

The number of basophil leucocytes, which have a high content of histamine, is usually decreased in urticaria, but not in asthma and atopic eczema. H. T. H. W.

A FURTHER STUDY OF THE KVEIM REACTION IN SARCOIDOSIS AND TUBERCULOSIS. H. L. Israel, M. Sones, H. Beerman and T. Pastras. (1958) *New Engl. J. Med.*, **259**, 365.

In an effort to determine the true value of the Kveim reaction in diagnosis, the authors tested 46 patients with sarcoidosis, on 36 of whom a biopsy at the site of injection was carried out.

Sarcoid granulomas were found in 13 ; non-specific granulomas in 8 and non-specific inflammation in 15.

The differences between these results and those obtained previously with similar material emphasize how greatly results may be influenced by the material used for testing, the interpretation of histological specimens and, to a much lesser degree, the type of patient being examined.

A. D. P.

SYSTEMIC LUPUS ERYTHEMATOSUS SIMULATING ACUTE SURGICAL CONDITION OF THE ABDOMEN. V. E. Pollak, W. J. Grove, R. N. Kark, R. O. Muehreke, C. L. Pirani and J. E. Steck. (1958) *New Eng. J. Med.*, **259**, 258.

This report described 14 patients with systemic lupus erythematosus in whom such severe abdominal symptoms appeared that consultation with a surgeon was required.

In 10 there was evidence of peritonitis and in 4 pancreatitis developed.

The symptoms were generally attributed to vascular changes typical of lupus erythematosus.

Large doses of cortico-steroids were found to relieve symptoms with 24–48 hours.

A. D. P.